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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102761 A1

(51) International Patent Classification[7]: C07C 209/52, 211/42

(21) International Application Number: PCT/FI02/00518

(22) International Filing Date: 14 June 2002 (14.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/298,088 15 June 2001 (15.06.2001) US
20011271 15 June 2001 (15.06.2001) FI

(71) Applicant *(for all designated States except US)*: **ORION CORPORATION FERMION** [FI/FI]; Koivu-Mankkaantie 6 A, FIN-02200 Espoo (FI).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **LAITINEN, Ilpo** [FI/FI]; Matinraitti 9 C 22, FIN-02230 Espoo (FI).

(74) Agent: **ORION CORPORATION**; Orion Pharma, Industrial Property Rights, Orionintie 1, FIN-02200 Espoo (FI).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102761 A1

(54) Title: A NOVEL PROCESS FOR THE PREPARATION OF (1S-CIS) -4-(3, 4-DICHLOROPHENYL) -1, 2, 3, 4 - TETRAHYDRO-N-METHYL-1-NAPHTHALENAMINE

(57) Abstract: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine (sertraline) is prepared by hydrogenating of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine in the presence of a dehalogenation inhibitor, e.g. triphenylphosphite or trimethylphosphite and a catalyst.

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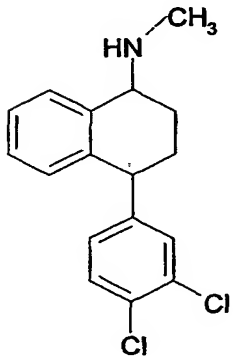
A NOVEL PROCESS FOR THE PREPARATION OF (IS-CIS) -4-(3,4-DICHLOROPHENYL) -1,2,3, 4- TETRAHYDRO-N-METHYL-1-NAPHTHALENAMINE

The present invention relates to a novel process for the preparation of (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine (sertraline) comprising hydrogenation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine.

BACKGROUND OF THE INVENTION

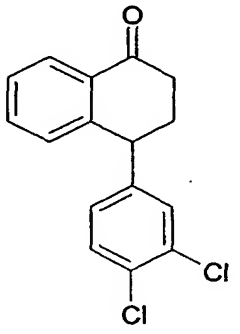
Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, which has a structure of formula I



I

is marketed in the form of its hydrochloride for the treatment of depression, obsessive-compulsive disorder and panic disorder.

The synthesis of sertraline is described in U.S. Patent no. 4,536,518. The process described comprises a condensation reaction of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone of formula II



II

with monomethylamine yielding N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine. This is further hydrogenated in the presence of palladium on carbon catalyst to form a mixture of cis- and trans-racemates of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine with the isomeric ratio of 70:30. The desired product is the cis isomer, and accordingly the trans isomer is a not desired byproduct which is classified as an impurity in the final product. Other impurities formed in the reaction are e.g. dehalogenation products, the amount of which depends e.g. on the temperature and pressure used in the hydrogenation and the quality of the imine starting material. The removal of the dehalogenation products is difficult.

Different solutions have been suggested to increase the formation of cis isomer and to prevent the dehalogenation reaction in the hydrogenation. In the process described in US 5,082,970 trans-isomer is treated with a basic equilibration agent like potassium tert.-butoxide to change it to cis-isomer. This however, requires an additional step in the synthesis. In WO 99/47486 copper containing catalysts are used to improve the ratio, and results as high as 98.5 % in favor of cis compound have been achieved. Nothing has, however, been said about the dehalogenation products formed. In WO 99/57093 a hydrogenation process with a palladium catalyst which has been pretreated with alkali halide has been described. The process described gives a cis/trans ratio of 85-95/15-5 (in %). The amount of dehalogenation side products is said to be below 0.5 %.

In US 3,474,144 there has been described the use of triphenyl phosphite or tritolyl phosphite as dehalogenation inhibitors in the catalytic reduction of aromatic chloronitro compounds. It has also been mentioned that the use of the inhibitors does not affect the original isomer ratio. In EP 292 682 there has been used organic esters of phosphoric acid together with hydrocarbyl-silanes to inhibit the dehalogenation during the catalytic reduction of aromatic nitro-halo-derivatives. The degree of dehalogenation lower than 1 % was reported. In Kosak, Catal. Org. Synth., 1980, vol. date 1978, p. 107-117, there has been described the use of phosphorous acid and some related compounds as dehalogenation inhibitors in the hydrogenation of haloaromatic nitro compounds. However, the use of the inhibitors of the present invention in the preparation of sertraline or in the hydrogenation of imine compounds has not been described.

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SUMMARY OF THE INVENTION

One object of the present invention is to provide an improved preparation method for cis-sertraline or a pharmaceutically acceptable acid addition salt thereof.

The other object of the present invention is the pharmaceutical composition comprising cis-sertraline or a pharmaceutically acceptable acid addition salt thereof made by the process of the invention.

These objects have been achieved by the inventor's surprising discovery that if some phosphorus compounds, specially esters of phosphorous acid, are used as dehalogenation inhibitors in the hydrogenation of the imine in the production of sertraline, the cis-trans ratio is improved. In addition the amount of dehalogenation products is diminished. The produced racemic cis-sertraline can be further resolved or crystallized directly to a pharmaceutically acceptable acid addition salt, e.g. hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of cis-sertraline comprising hydrogenating N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine in the presence of a catalyst and a dehalogenation inhibitor to achieve cis-racemate of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine.

By using the hydrogenation process of the present invention the ratio of cis:trans isomers is improved to as high as 97:3 and the formation of dehalogenation byproducts may be reduced to even less than 0.1 %. No further purification process is needed before resolution or crystallization. This is achieved by using the inhibitors of the invention in the hydrogenation process.

Cis-sertraline is prepared starting from 4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenone (tetralone), which can be prepared by methods known in the art, e.g. as decsribed in US 5,019,655. Tetralone is reacted with monomethylamine to form an imine, which can be performed by methods known in the art, e.g. as described in US 4,536,518. The imine obtained is further hydrogenated to cis-racemate of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine

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in the presence of a catalyst and a dehalogenation inhibitor of the invention. From this mixture, the cis-compound can be either resolved by e.g. mandelic acid or 10-camphorsulphonic acid to afford cis-(+)-sertraline and crystallized as a base or a pharmaceutically acceptable acid addition salt, e.g. hydrochloride, or the racemic cis-sertraline can be crystallized as a base or as a pharmaceutically acceptable salt.

The hydrogenation of the imine is performed in the presence of a catalyst and an inhibitor, which is selected from the group consisting of hypophosphorous acid, esters of hypophosphorous acid, phosphorous acid, esters of phosphorous acid, phosphine and substituted phosphines. Suitable inhibitors are e.g. mono-,di- and triesters of phosphorous acid, preferably trimethyl phosphite, triphenyl phosphite or tritolyl phosphite. Examples of suitable phosphines are e.g. trimethylphosphine, triethylphosphine, triisopropylphosphine, tritolylphosphine and tribenzylphosphine. The amount of the inhibitor used in the process is typically 0.5 - 10 mol %, preferably 3 - 5 mol %, based on the number of moles of the metal in the catalyst used. The catalyst used can be any suitable catalyst known in the art, e.g. palladium on carbon, palladium on graphite, palladium on carbon paste or PtO_2. The catalyst is typically used in the amount of 0.1 - 1.0 % (w/w, calculated as the pure metal in the catalyst) based on the weight of the imine used. The hydrogenation may be carried out in an organic solvent, which can be any suitable protic or aprotic solvent or mixtures thereof. Examples of solvents are e.g. dimethylformamide (DMF), esters like ethyl acetate, chlorinated hydrocarbons like methylene chloride or chloroform, or alcohols like methanol, ethanol or isopropanol. Preferably a lower alcohol, e.g. methanol or ethanol or their mixture with DMF is used as a solvent.

The reaction can be carried out at a temperature of 0-100 °C, preferably at 20 - 50 °C. The hydrogen pressure used is from 1 to 50 bar, preferably from 2 to 5 bar.

The reaction time can vary from half an hour to 24 hours depending on the catalyst used, on hydrogen pressure, on the reaction temperature and on the equipment used. Preferably the hydrogenation time is about 2 to 6 hours.

The following examples merely illustrate the invention and they are not to be construed as limiting.

EXAMPLE 1

Cis-(1S)(1R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenylidene]-methanamine (50 g), methanol (300 ml), palladium on graphite 5 % (2.5 g) and trimethyl phosphite (0.004 g) are charged into a reaction vessel. The mixture is hydrogenated at 5 bar overpressure of hydrogen for 5 hours at about 40 °C. The catalyst is removed by filtration and the cake is washed with methanol. The cis:trans ratio is 97:3. The amount of dehalogenation byproducts is < 0.1 %. The reaction mixture can be used directly in the resolution step or crystallized as HCl salt.

EXAMPLE 2

(1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride (Sertraline hydrochloride)

The reaction mixture containing the rasemic compound from the previous step is resolved by mandelic acid and finally crystallized as sertraline hydrochloride. The total yield is 19.8 g (70 % of theoretical (+)-enantiomer). Analytical results: HPLC-purity is 99.9 %, trans-isomer < 0.1 % and dehydrohalogenation products < 0.1 %. Optical purity is 99.9 %.

EXAMPLE 3

Cis-(1S)(1R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine

N-[4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine (40 g), dimethylformamide (150 ml), methanol (150 ml), palladium on graphite catalyst (4 g) and triphenyl phosphite (0.0010 g) are charged into a reaction vessel. The mixture is hydrogenated for 5 hours under 5 bar overpressure of hydrogen at 20-25 °C. The catalyst is removed by filtration and the cake washed with methanol. The cis:trans ratio is 96:4 and the amount of dehalogenation byproducts is 0.5 %.

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EXAMPLE 4

Cis-(1S)(1R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1-(2H)-naphthalenylidene]-methanamine (50 g), methanol (400 ml), palladium on graphite 5 % (5 g) and triphenyl phosphine (0.014 g) are charged into a reaction vessel. The mixture is hydrogenated at 5 bar overpressure of hydrogen for 3 hours at about 35 °C. The catalyst is removed by filtration and the cake is washed with methanol. The cis:trans ratio is 97:3. The amount of dehalogenation byproducts is 0.2 %. The reaction mixture can be used directly in the resolution step or crystallized as HCl salt.

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CLAIMS

1. A process for the preparation of cis-sertraline comprising hydrogenating N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine in the presence of a catalyst and a dehalogenation inhibitor to obtain cis-racemate of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine.

2. A process according to claim 1 wherein the dehalogenation inhibitor is selected from the group consisting of hypophosphorous acid, esters of hypophosphorous acid, phosphorous acid, esters of phosphorous acid, phosphine and substituted phosphines.

3. A process according to claim 1 wherein said dehalogenation inhibitor is an ester of phosphorous acid.

4. Process according to claim 3 wherein said dehalogenation inhibitor is triphenyl phosphite or trimethyl phosphite or tritolyl phosphite.

5. A process according to any of claims 1 to 4 wherein the dehalogenation inhibitor is used in the amount of 0.5 to 10.0 mol % based on the number of moles of metal in the catalyst used.

6. A process according to claim 5 wherein the dehalogenation inhibitor is used 3 to 5 mol % based on the number of moles of metal in the catalyst used.

7. A process according to claim 1 wherein said catalyst is a palladium or a platinum catalyst.

8. A process for the preparation of (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine or acid additon salt thereof comprising:
hydrogenating N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine in the presence of a catalyst and a dehalogenation inhibitor to obtain cis-racemate of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine:
and resolving said cis-racemate of 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine to obtain the (+)enantiomer of cis- 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine.

9. The process according to claim 8, further comprising crystallizing said (+)enantiomer of cis-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine as a base or as an acid addition salt.

10. The process according to claim 9 wherein the acid addition salt is hydrochloride.

11. A process according to claim 8 wherein said inhibitor is selected from the group consisting of hypophosphorous acid, esters of hypophosphorous acid, phosphorous acid, esters of phosphorous acid, phosphine and substituted phosphines.

12. A process acoording to claim 10 wherein said dehalogenation inhibitor is an ester of phosphorous acid.

13. A process accoding to claim 11 wherein said ester is triphenyl phosphite or trimethyl phosphite or tritolyl phosphite.

14. Pharmaceutical composition comprising cis-sertraline or pharmaceutically acceptable acid addition salt thereof prepared by the method of any of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 02/00518

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 209/52, C07C 211/42
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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24 Sept 2002	14 10 2002
Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer EVA JOHANSSON/EÖ Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No.
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